REMARKS

Claims 1-22 have been cancelled and claims 23-37 have been added. The claims now present in this application are claims 23-37.

Accompanying this Amendment is a Substitute Declaration by the inventors in compliance with 37 C.F.R. 1.497(a) (2). In this Substitute Declaration, the international application PCT/IB04/01723, filed May 19, 2004 is specifically identified. As set forth in this Substitute Declaration, the captioned application was filed as a national phase application of PCT 11B04/01723. Therefore, this Substitute Declaration corrects the deficiencies set forth in the outstanding Office Action.

Applicants have presented new claims 23 through 37 to replace claims 1 through 22. The newly added claims find support in the instant application as outlined below. Claim 23 presents claim 1 so that the definition of R^2, R^3, R^4, R^5 and R^6 are limited in accordance with the formula set forth on page 45 of the instant specification. Both in claim 23 and in the compound set forth on page 45, R^2, R^3, R^4, R^5 and R^6 are defined as hydrogen. The definition of R^1 in claim 23 has been limited to specifically hydrogen, hydroxy, lower alkyl, cyano, lower alkyl, lower alkylcarbonyl, lower alkoxy-carbonyl or lower carboxy-lower alkyl since these are among the substituents set forth in claim 1. In Claim 23, the groups which may be optionally substituted on the heteroaromatic or aromatic ring are specifically enumerated. These substituents are set forth on page 15, lines 15-35 and page 24, Lines 10-21 of the instant specification.

In Claims 25-26 various specific compounds are set forth. These specific compounds find support in the instant specification by means of their number given in these claims . For example in claim 25, compound 1 is specifically the compound found in Example 1 of this application, compound 14 is specifically the compound found in Example

14 of this application. Therefore the numbers set forth in these claims refer to the examples in the instant specification in which specific support for each of these compounds is set forth.

Claims 35 and 36 present the limitations of claims 16 and 17 in independent form. On page 10 of the Office Action, it is indicated that claim 16 and 17 would be allowable if written in independent form. In this manner, claims 36 and 37 are claims 16 and 17 written in independent form.

The claims have been rejected under 35 U.S.C. 112, second paragraph. This rejection has been respectfully obviated by the filing of these new claims. In these new claims "optionally substituted phenyl carbonyl" has been amended so that the specific substituents which can be substituted on the phenyl carbonyl ring are designated. In addition terms such as "derivative thereof" or "protected derivative" have been eliminated in the newly presented claims. In addition, the term "and/or" has been changed in these newly presented claims to "or". Claim 19 which is directed to as a process has been cancelled. Furthermore, the "use claims" present in the originally filed claims are not present in the claims as now presented.

Attached hereto are two reports. Comparative Report I and Comparative Report II. Both Comparative Reports I and II present tests comparing the claimed compound of this invention against the compounds set forth in the cited patent publication U.S. 2004/0034037, assigned to Vertex Pharmaceuticals ("the Vertex patent publication"), as an anti tumor agent for the inhibition of cell growth-proliferation. In the comparative studies the IC50 values of the compounds of this invention and the compounds of the patent publication U.S. 2004/0034037 Vertex patent publication as anti-tumor agents in inhibiting the cell growth-proliferation of three different cancer cell lines were determined.

Comparative Report I compares the claim compounds of this invention with Example 26 set forth on page 8 of the Vertex patent publication. The results of Table 1 of Comparative Report 1, demonstrate that the Vertex compound is inactive against these standard cancer cell lines. This is seen from the fact that the Vertex compound has IC50 value of greater than 10,000 nM in all assays. On the other hand, the claimed compounds of this invention are highly active against all of these cancer cell lines since, since they have IC50 values of lower than 200 nM against all of these cell lines. This report demonstrates that the compounds of this invention have new and unexpected properties, particularly anti tumor activity when compared to the compound of Example 26 of the Vertex patent publication.

Comparative Report II presents results which demonstrate the anti-proliferation activity on cancer cells of the compounds of this invention as compared to Examples 1, 4, 6, 21, 24, 15, 20, 12, 13 and 19 of the Vertex patent publication. As seen from the results of the test data in Comparative Report II, theses Vertex compounds are inactive as anti tumor agents against the standard cancer cell lines since they have IC50 values greater than 1,000 nM in all assays. On the other hand this test data shows that the compounds of this invention are active against all of these cell lines since they have IC50 values below 50 nM. In fact, these Vertex compounds are the very same compounds set forth on page 9 of the outstanding Office Action as being the closest compounds in the Vertex patent publication to the claimed compounds of this invention. In this manner, the comparative test data set forth in Comparative Report I and Comparative Report II demonstrate the new and unexpected properties anti tumor properties of the compounds of this invention when compared to the closest compounds set forth in Vertex patent publication.

The claims have been rejected as unpatentable under 35 U.S.C. 103(a) as being unpatentable over Vertex patent publication, U.S. 2004/0034037. This rejection is respectfully traversed.

The newly presented claims of this invention are directed to benzimidazoles where the fused ring of the benzimidazole is attached by a two membered chain to an aromatic or heteroaromatic ring. The aromatic ring can be phenyl or napthyl and the heteroaromatic ring can be thienyl, pyridinyl or pyridazinyl. In the claim compounds, the nitrogen atom of the fused benzimidazole ring is connected to the aromatic or heteroaramatic ring by a two membered chain, one of the members being either oxygen or carbonyl. This structural configuration is not disclosed in the Vertex patent publication. In fact, in claims 24-36, this bridge is claimed as containing a carbonyl member. None of the bridges disclosed in the Vertex patent publication have such a carbonyl member.

The basis for this rejection is that the generic Formula 1 and 1A of the Vertex patent publication encompass within the myriad of combinations and permutations of the various substituents set out, the claimed compounds of this invention. When one looks at the specific compounds set forth in this Office Action, none of these compounds are benzimidazoles having the nitrogen of its fused benzimidazole ring connected to an aromatic or heteroaromatic ring by means of a two membered bridge, one of the members being a carbonyl or oxo. None of the compounds set forth in the Vertex patent in the Office Action or anywhere else contain this structural configuration of an aromatic ring or heteroaromatic ring connected by the bridge to the nitrogen atom of a fused benzimidazole ring. The bridges utilized in the Vertex patent publication for connecting an aromatic or heteroaromatic ring do not contain a carbonyl or oxo member. In this case, the Vertex bridges are amide bridges or alkylene bridges not carbonyl or oxo bridges as claimed.

Therefore, the Vertex patent does not disclose any specific compounds having the structural configuration as claimed in the instant application much less any compound with a configuration having a carbonyl containing bridge such as present in claims 24-36.

In holding that it is sufficient for an obviousness rejection, under 35 U.S.C. 103, that the compounds of this invention fall within the generic disclosure of the Vertex patent publication, it is stated on page 8 of the Office Action that:

> The indiscriminant selection of 'some' among "many" is *prima facie* obvious, *In re Lemin*, 141 USPQ 814 (1964).

In re Lemin, supra, does not hold the compounds of this invention *prima facie* obvious in view of the fact that they are encompassed within the vast the myriad of combinations and permutations of various substituents of a generic formula disclosed in the prior art . In fact the CCPA in the *Lemin case , supra,* held that Lemin overcame the prior art which disclosed that the total number of carbon atoms in the alkyl substituants, was from 3-23 by limiting the number of the carbon atom in his claimed substituants to from 5 to 12. Therefore the difference between the genius disclosed by the prior art in the *Lemin case , supra,* was in the total number of carbon atoms and it was this limitation which was the critical factor establishing the patentability of Lemin's claimed compounds containing an alkyl substituent of from 5-12 carbon atoms. The *Lemin case ,supra* , did not deal with the situation where the claimed compounds were encompassed within the myriad of combinations and permutations of various substituents for a generic formula set forth by the prior art. It was not the case of choosing the proper combination and permutations of substituents within the generic disclosure as in the present situation Therefore the *Lemin case ,supra* is not applicable to the present situation.

It has been established that even though the claimed compound are encompassed within the combinations and permutations the definition of various substituents for a generic formula disclosed by the prior art, this is not sufficient to establish a *prima facie* of obviousness of the claimed compounds . Please note the decision of the CCPA in *In re Baranauckas*, 228 F.2d 416 (CCPA 1955) which involved the issue of *prima facie* obviousness in view of prior art encompassing the claimed compounds within the myriad of substituents set forth therein. As stated by the CCPA in *Baranauckas* in discussing *prima facie* obviousness:

> What the precise boundary lines are, we are unable now to discern. Certainly they do not extend so far as to permit publication of theoretical lists of hundreds or thousands of possible compounds to deny patent protection on such compounds to those who actually discovered them later. 228 F. 2d at 416, -

Also, attention is directed to the decision of the Court of Appeals for the District of Columbia *in E.I. DuPont de Nemours & Co. v. Ladd, 328 F.2d 547.* In *the DuPont case, supra*, the Court of Appeals held that the fact that the claimed compound came within the scope of the prior art Markush Group by selecting the proper combination of substituents within the generic definition of the prior art did not constituted *prima facie* obviousness. In holding that the prior art did not suggest or render obvious the claimed compounds, the Court of Appeals stated:

> Certainly the Alder patent, allowing as it did an infinite number of possibilities, would be minimally described as an implicit 'publication of theoretical lists of hundreds or thousands of possible compounds', and thus would not be an appropriate anticipation of a later patent application for a specific compound.

Based on the foregoing it is clear that the Vertex publication does not constitute a *prima facie* case of obviousness of the claimed compounds. The decision of the Court of Appeals in the *DuPont* case, *supra,* has been adopted by the CCPA in *In re Luvisi* , 342 F. 2d 102

(CCPA 1965) and by the Board of Appeals of the U.S. Patent and Trademark Office in *Ex parte Broadbent, et al,* 150 U.S.P.Q. 468 (1966).

Even with the fact that the claimed invention is not rendered *prima facie* obvious by the Vertex patent publication, the claims of this invention have new and unexpected properties anti-tumor as shown from Comparative Report I and Comparative Report II. The compounds of this invention have anti-tumor properties since they have anti-proliferative and growth activity against tumor cells. The Vertex compounds are not disclosed as having anti-tumor activity compounds of this invention. The Vertex compounds are disclosed as being useful as inhibitors of GSK-3 and Lck protein kinases. There is no disclosure in Vertex patent publication and that their disclosed compounds are active as anti tumor agents, much less in the manner of the claimed compounds of this invention. As seen from the Comparative Report I and Comparative Report II, the claimed compounds of this invention have new and unexpected properties when compared to the compounds disclosed in the Vertex patent publication. Therefore, the claimed compounds are not rendered obvious by the Vertex reference but also have new and unexpected properties.

Based upon the foregoing, it is submitted that all of the claims in this application are allowable.

Correspondence and Fees

Please charge the Petition for Three Month Extension of Time fee of $510.00 to Deposit Account No. 03-3839. No fees are believed to be necessitated by the instant response. However, should this be in error, authorization is hereby given to charge Deposit Account No. 03-3839 for any underpayment, or to credit any overpayments.

Please address all correspondence to Intellectual Property Docket Administrator, Gibbons, P.C., One Gateway Center, Newark, New Jersey 07102-5310. Telephone calls should be made to William H. Epstein at (973) 596-4607 and fax communications should be send directly to him at (973) 639-6397.

Respectfully submitted,

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basilea
PHARMACEUTICA

COMPARATIVE REPORT II

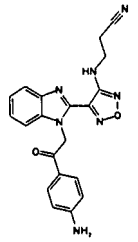
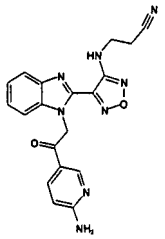
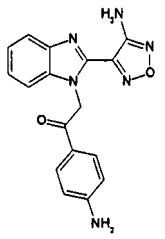
Case 22009 - Comparative Data

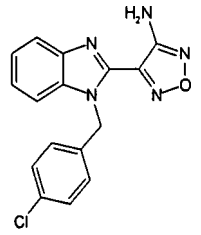
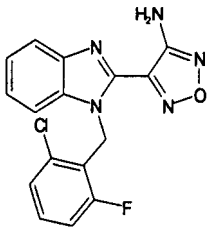
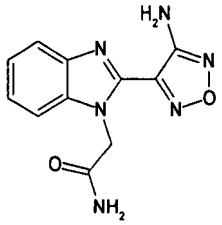
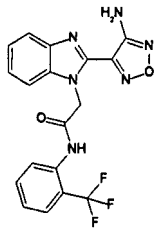
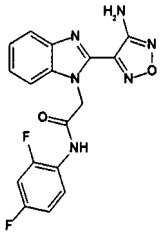
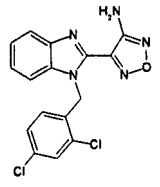
Antiproliferative Activity on Cancer Cells

The IC50 values for the inhibition of cell growth/proliferation have been determined versus three different cancer cell lines. The results are shown in Table 1.
Representative Basilea compounds BAL0027862, BAL0027864 and BAL0028696 exhibit IC50 values below 50 nM against these cell lines, whereas the IC50 values for the Vertex comparator compounds were above 1000 nM in all assays.

Experimental conditions: Growth/Proliferation (GP) of 3 different cell lines representing clinically relevant tumor types (HeLa: human cervical squamous cell carcinoma, HT1080: human fibrosarcoma, HT-29: human colorectal adenocarcinoma) was determined by the crystal violet staining method according to Gillies, R.J. et al. (Determination of Cell Number in Monolayer Cultures, Analytical Biochemistry, 159: 109-113 (1986)). Crystal violet retained by the fixed cells was quantified by measuring absorption at 590 nm. IC50 values were calculated by fitting the normalized data to a sigmoidal dose-response model with a variable slope.

Table 1. Antiproliferative activity; IC50 values (nM) versus cancer cell lines

Corporate ID	Basilea WO 2004/103994	Vertex US 2004/0034037	GP HeLa	GP HT1080	GP HT-29
BAL0027862 	Ex. 58	-	18	15	11
BAL0027864 	Ex. 79	-	23	14	17
BAL0028696 	Ex. 50	-	44	27	33

BAL0070367 	-	Ex. 1	> 1000	> 1000	> 1000
BAL0070368 	-	Ex. 4	> 1000	> 1000	> 1000
BAL0070369 	-	Ex. 6	> 1000	> 1000	> 1000
BAL0070370 	-	Ex. 21	> 1000	> 1000	> 1000
BAL0070371 	-	Ex. 24	> 1000	> 1000	> 1000
BAL0029349 	-	Ex. 15	> 1000	> 1000	> 1000

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COMPARATIVE REPORT I

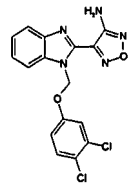
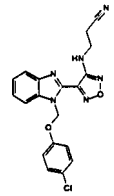
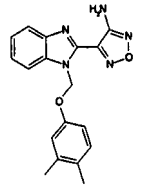
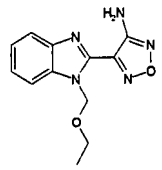
Case 22009 - Comparative Data - Ether derivatives

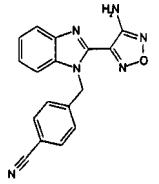
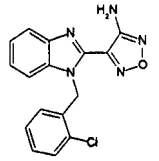
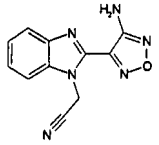
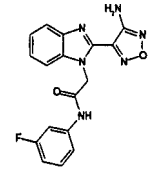
Antiproliferative Activity on Cancer Cells

The IC50 values for the inhibition of cell growth/proliferation have been determined versus three different cancer cell lines. The results are shown in Table 1.
Representative Basilea compounds BAL0028746, BAL0028747 and BAL0028819 exhibit IC50 values below 200 nM against these cell lines, whereas the IC50 values for the Vertex comparator compound BAL0070413 were above 10'000 nM in all assays.

Experimental conditions: Growth/Proliferation (GP) of 3 different cell lines representing clinically relevant tumor types (HeLa: human cervical squamous cell carcinoma, HT1080: human fibrosarcoma, HT-29: human colorectal adenocarcinoma) was determined by the crystal violet staining method according to Gillies, R.J. et al. (Determination of Cell Number in Monolayer Cultures, Analytical Biochemistry, 159: 109-113 (1986)). Crystal violet retained by the fixed cells was quantified by measuring absorption at 590 nm. IC50 values were calculated by fitting the normalized data to a sigmoidal dose-response model with a variable slope.

Table 1. Antiproliferative activity; IC50 values (nM) versus cancer cell lines

Corporate ID	Basilea WO 2004/103994	Vertex US 2004/0034037	GP HeLa	GP HT1080	GP HT-29
BAL0028746 	Ex. 92	-	60	48	43
BAL0028747 	Ex. 93	-	150	104	62
BAL0028819 	Ex. 101	-	93	77	59
BAL0070413 	-	Ex. 26	> 10000	> 10000	> 10000

BAL0029354 	-	similar to Ex. 20	> 1000	> 1000	> 1000
BAL0030784 	-	Ex. 12	> 1000	> 1000	> 1000
BAL0030785 	-	Ex. 13	> 1000	> 1000	> 1000
BAL0030786 	-	similar to Ex. 19	> 1000	> 1000	> 1000